

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Elliot Ehrich
Application No.: 13/871,534 Group No.: 1627
Filed: April 26, 2013 Examiner: Carter, Kendra D.
Confirmation No.: 5842
For: NALTREXONE LONG ACTING FORMULATIONS AND
METHODS OF USE

APPEAL BRIEF

Mail Stop Appeal Briefs Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is being filed pursuant to 37 CFR §41.37. The required sections (i-v) under 37 CFR §41.37(c)(1) are set forth below under separate headings.

(i) The Real Party In Interest

The real party of interest in this appeal is the assignee, Alkermes Pharma Ireland Limited by virtue of the assignment recorded on October 16, 2015 at Reel 036809 and Frame 0447.

(ii) Related Appeals, Interferences, and Trials

There are no related appeals, interferences, or trials at this time known to the Appellant, the assignee or its representative which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(iii) Summary of Claimed Subject Matter

Independent claim 1 recites a method for treating an individual in need of naltrexone comprising the step of administering by intramuscular injection a long acting formulation comprising naltrexone to the individual wherein the serum AUC of

{{/4000/3010US3/00264828/v2}}

naltrexone is at least about two times greater than that achieved by 50 mg/day oral administration, wherein the long acting formulation of naltrexone is administered only once during at least a two week period, and comprises between 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone. Support for claim 1 is found on page 3, lines 7-11 and 29-31; page 4, line 1; page 6, lines 3-6 and 24-31; and page 7, line 1.

Claim 6 depends directly from claim 1 and further recites that the long acting formulation releases naltrexone for a period of about four weeks. Support for claim 6 is found on page 6, lines 24-25.

Claim 7 depends directly from claim 1 and further recites that the long acting formulation is administered in a dose of about 380 mg of naltrexone. Support for claim 7 is found on page 4, lines 1-2.

Claim 11 depends directly from claim 1 and further recites that the long acting formulation is administered over a period of about 24 weeks or longer. Support for claim 11 is found on page 2, lines 19-22.

Claim 14 depends directly from claim 1 and further recites that the individual is an individual afflicted by alcohol dependency. Support for claim 14 can be found on page 7, lines 21-24.

Claims 16-17 depend directly from claim 1 and further recite that the long acting formulation comprises a polylactide polymer, a poly lactic acid polymer, or a polylactide-co-glycolide polymer. Support for claims 16 and 17 can be found on page 4, lines 10-12.

Claim 18 depends directly from claim 1 and further recites that the naltrexone is present in the long acting formulation at a concentration of about 35% by weight. Support for claim 18 can be found on page 5, lines 24-27.

Claim 22 depends directly from claim 11, which depends directly from claim 1, and further recites that the method of claim 11 further comprises a second administration of the long acting formulation comprising naltrexone at least about 28 days after the first administration. Support for claim 22 can be found on page 7, lines 5-8.

(iv) Argument

A. Claims 1, 6, 7, 11, 14, 16-18, and 22 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Heinala et al. (Journal of Clinical Psychopharmacology, 2001, vol. 21, pp. 287-292) as applied in claim 1 in view of Bartus et al. (Neuropsychopharmacology, 2003, vol. 28, pp. 1973-1982), Leavitt (Addiction Treatment Forum Ed., 2002, pp. 1-8), and Johnson (Therapeutics and Clinical Risk Management, 2007, vol. 3, no. 5, pp. 741-749).

Claim 1

The Examiner asserts that one of ordinary skill in the art at the time of the invention would have found it obvious and been motivated to modify the method of Heinala et al. and the claimed amounts of naltrexone administered according to the teachings of the secondary references. [Final Office Action dated March 17, 2015, page 7, first paragraph, through page 8; Upheld in Advisory Action dated August 4, 2015, page 2, first paragraph]

The Examiner continues on page 8 of the Final Action, asserting it is considered obvious that “once one administers the formulation and method of Heinala et al. in view of Bartus et al. and Leavitt, one would obviously obtain the pharmacokinetics claimed.” Appellant respectfully disagrees.

Many of the facts related to this appeal are not in dispute.

1. Heinala does not teach long acting naltrexone formulations, intramuscular administration, or the pharmacokinetic profile

Heinala is relied upon to show that oral naltrexone (50 mg/day) can be used to treat alcohol dependence in non-abstinent alcoholics.

It is admitted that Heinala does not teach (1) administration of a long acting form of naltrexone (2) to achieve a pharmacokinetic profile of at least 2 times the oral dosage (as measured by the serum AUC) (3) by injection (4) on at least a biweekly or monthly schedule (5) over a period of 24 weeks or more of (6) formulations that comprise a

polylactide or PLGA. Thus, it appears to be admitted that Heinala does not teach any material limitation of the claim (the formulation, mode of administration, dosing regimen, dose or pharmacokinetic profile).

The Examiner does not dispute that Heinala also teaches oral administration of naltrexone on an as needed basis when the craving for alcohol is high (see the last 4 lines of the article) and that Heinala warns against the possibility that long term naltrexone use may produce supersensitivity of the opioid receptors and other side effects. Thus, the fact that Heinala also has teachings away from the claimed invention also does not appear to be in dispute.

The Examiner then relies upon three secondary references to teach these missing limitations in an effort to arrive at the claimed invention.

2. Leavitt does not teach long acting injections

Leavitt is relied upon to teach that naltrexone can be orally administered at doses ranging from 12.5 mg/day to 150 mg/day. Leavitt is a review article of several clinical trials of orally administered naltrexone. The Abstract suggests flexible dosing and, like Heinala, on an “as needed basis.”

Leavitt does not teach that intramuscular injection of a 380 mg long acting formulation can achieve a serum AUC of twice 50 mg/day oral dosing. Nor does Leavitt teach that such a dose by injection (either 380 mg, for example, or twice the AUC of oral naltrexone) is desirable. In fact, since a long acting formulation would not be “flexible dosing” on an “as needed basis,” it does not appear to be disputed that Leavitt, like Heinala, provide teachings away from the claimed invention.

3. Bartus does not teach the desired dosing or a method of manufacture

Bartus is relied upon to show a long acting formulation comprising PLGA and about 35% naltrexone, called Vivitrex® microspheres. Bartus administered 50 mg/kg of the microspheres to Sprague Dawley rats and repeated the dose after 34 days to a group of these rats.

It is not disputed that Bartus does not teach (1) that it is desirable to administer naltrexone to achieve an AUC that is at least twice that of the 50 mg/day oral dose in humans, (2) the human dose in mg of naltrexone, (3) how one would select a human dose from the rat dose, or (3) a method for manufacturing Vivitrex® microspheres.

Therefore, it is not disputed that Bartus does not teach the missing limitations of the claims relating to the human dose and pharmacokinetic profile or a method of manufacturing the product.

4. Johnson is not prior art and does not teach how to make the product

Johnson was published in 2007. The effective filing date for the present claims is 2004. It is not in dispute that Johnson is not available as prior art.

In spite of this fact, the Examiner states that Johnson is “an evidentiary art to prove what is in VIVITREX.” [Advisory Action, Page 5] and that Vivitrex® is naltrexone formulated into poly-(lactide-co-glycolide) microspheres. [Final Action, page 11, first paragraph]. It appears that the Examiner admits that Bartus does not teach what is in Vivitrex® microspheres and that one must resort to literature that is not prior art.

Johnson is not relied upon, and cannot be relied upon, to provide a teaching of the state of the art at the time of the invention. Additionally, while Johnson does state that Vivitrex® microspheres contain PLGA and naltrexone, like Bartus, Johnson also does not provide a teaching of how to make Vivitrex® microspheres.

5. 2003 Alkermes Press Release is improperly cited, is not prior art and does not teach how to make the product

In the Advisory Action dated August 4, 2015, the Examiner asserts that the Alkermes Press Release of December 8, 2003 teaches a 380 mg naltrexone injectable suspension with the poly-lactide co-glycolide polymer can be administered once a month to humans. [Advisory Action, page 2, third paragraph; page 5, lines 1-4; page 8, last seven lines].

Firstly, it is not clear if the Examiner is relying upon the Press Release in the rejection as it does not appear in the statement of the rejection. If the Press Release is being relied upon, the rejection is a new ground of rejection and maintaining finality was improper. Appellant has a right to rebut the newly relied upon reference. MPEP Sec. 706.07(e) and 1207.03.

Secondly, the Press Release is obviously derived from Appellant's invention (as evidenced by Evidence Documents #1, #2, and #4 -7). The instant application has a priority date of April 22, 2004. While Appellant has not been afforded the opportunity to present a Declaration by Inventor Ehrich explicitly addressing the point (e.g., under 37 CFR 1.131 or a so-called Katz declaration under 35 USC 1.132), it is apparent on the face of the underlying facts. Thus, this reference is not available as prior art as it is not a publication by others.

Thirdly, while the Press Release describes a 380 mg dose of Vivitrex microspheres, it is silent as to (1) how to make the microspheres and (2) the claimed serum AUC of at least 2 times that of oral naltrexone at 50 mg/day.

6. The pharmacokinetic profile of a drug product is dependent on the dose and formulation

It is not disputed that the pharmacokinetic profile of a 380 mg. dose of Vivitrex® microspheres is different than the pharmacokinetic profile of a 190 mg. dose of Vivitrex® microspheres when administered to humans. (Evidence Document 1; Pages 1-2).

It is not disputed that the pharmacokinetic profile of a 380 mg. dose of Vivitrex® microspheres is different than the pharmacokinetic profile of a dose of naltrexone long acting microspheres made with PLA as disclosed by US Patent 6,306,425 to Tice et al. (Evidence Document 4; Pages 2-3 and Evidence Document 8). The Examiner concedes this fact in the Advisory Action, Page 10.

Therefore, it is not in dispute that the pharmacokinetic profile of naltrexone long acting microspheres is dependent on the dose and formulation and is simply not inherent

to any dose of any PLGA microsphere containing naltrexone.

The Examiner appears to ignore the fact that the result (superior efficacy and pharmacokinetic profile) is dose dependent and Bartus does not teach a human dose. That is, the administration of Bartus' microspheres will not inherently achieve the claimed pharmacokinetic result (a serum AUC at least two times the 50 mg/day oral dose) at all doses. One must choose the dose to achieve efficacy and the pharmacokinetic result. It is clear error for the Examiner to supply what is missing from Bartus (e.g., the human dose and pharmacokinetic profile) with Johnson (which is not prior art) to dismiss the evidence of unexpected results as inherent in the microspheres.

7. No prior art reference teaches the claimed dose or suggests selecting the pharmacokinetic profile

A close review of each of the *prior art* references relied upon in the statement of the rejection (Heinala, Leavitt, and Bartus) establishes that **none** disclose the administration of a long acting formulation having 160 to 240 mg or 310 to 480 mg naltrexone to an individual to achieve a serum AUC of at least 2 times that of oral naltrexone at 50 mg/day.

Heinala teaches oral dosing at 50 mg/day daily and, after several weeks, as needed when alcohol craving is high. Leavitt (a review of oral clinical trials) appears to echo the teachings of Heinala that efficacy can be achieved by oral dosing on an as needed basis. These teachings advocate for **less than** a 50 mg/day oral dose after several weeks and that **daily** dosing is unnecessary. These teachings advocate against administering a long acting formulation because a long acting formulation cannot achieve a dosing "as needed," much less an injection that achieves serum plasma levels at least twice the oral dose.

Bartus advocates for long acting formulations. However, this article does not promote dosing to achieve serum AUCs of at least twice the approved oral dosing.

While Johnson teaches the dosing for Vivitrex® microspheres at 380-400 mg and reports favorable pharmacokinetic results (albeit the serum AUC is not disclosed), the

article is not prior art and is, with respect to Vivitrex®, clearly derived from the Appellant's own work.

No reference teaches how to make a naltrexone long acting formulation that will achieve the pharmacokinetic profile as claimed at the claimed doses. No reference teaches that it would be desirable to do so.

8. The CDER establishes that the human dose is not a simple extrapolation from the rat dose of Bartus

In the Final Office Action, the Examiner relied upon the CDER Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005, pp. 1-7 (the "CDER") to extrapolate a rat dose to a human dose (attached hereto as Evidence Document #3). She maintains that she is continuing to rely on the CDER in the Advisory Action, not as a reference in the rejection, but rather as evidence that it is within the skill of the art to determine dosages based on animal studies. [Final Action, page 10, last paragraph through page 11; Advisory Action, page 7, middle of last paragraph; Advisory Action page 8, 10 lines from bottom of page]

Appellant asserts that the Examiner is, in fact, relying on the document for evidence and that the rejection is improperly stated. In addition, it does not provide the requisite teaching as detailed below.

In the Final Office action, the Examiner made certain mathematical calculations in an attempt to show that the claimed dose was an obvious extrapolation from Bartus' rat dose. Appellant challenged the factual bases for the allegations made in the Final Rejection. The Examiner admits in the Advisory Action that her calculations found on page 10 of the Final Action are incorrect.

The Examiner asserted the claimed amounts of naltrexone for human injection are obvious to determine.

For instance, the conversion of [a] mouse (i.e. rat) to human mg/kg dosages according to the CDER (Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005, pp. 1-7) is to multiply the animal dose by 0.08 (see page 7, Table 1).” [Final Action of March 17, 2015, page 10, last paragraph]

Appellants established, to the Examiner’s satisfaction, that this was factually incorrect.

a. The Examiner’s calculations were incorrect

The Examiner’s statement relied upon mistaken factual assumptions.

i. Mice are not rats.

The Examiner states the conversion of a “mouse (i.e. rat) to human mg/kg dosages... is to multiply the animal dose by 0.08.” A rat is not a mouse (as evidenced by the fact that the two animals are listed separately in the Table) and the conversion factors differ. Table 1 lists the rat conversion factor as being twice that of the mouse conversion factor. Thus, contrary to the Examiner’s statement, Table 1 on page 7 of CDER guidance teaches 0.16 as a conversion factor for rat-to-human, not 0.08.

In fact, Appendix B of the CDER makes clear that the “rat,” in this instance, is a small rat and the conversion is not linear based on weight. Appendix B states that the k_m (the inverse of the conversion factor) of a 100 g rat is 5.2 (conversion factor is 0.19) and 7.0 for a 150 g rat (conversion factor is 0.16) listed in Table 3. Bartus, on the other hand, used Sprague Dawley rats weighing 450 g, more similar to the guinea pig weight (400 g) listed in Table 3, with a conversion factor of 0.216. If one were to use the guinea pig conversion, the 50 mg/kg of a 400 g animal dose is 10.8 mg/kg or 648 mg for a 60 kg human.

Thus, *if* one were to assume that these conversion factors can be applied to depot formulations of naltrexone and that Bartus’ rat dose was appropriate to extrapolate to a

human dose, a 50 mg/kg *rat* dose would convert to 8 mg/kg in a human or 480 mg for the assumed 60 kg human (see Footnote a), and not 4 mg/kg as asserted by the Examiner.

The Examiner's factual mistake that the claimed dose is a simple extrapolation of Bartus's rat dose to a human dose is clearly erroneous because a mouse is not a rat.

ii. Humans are assumed to be 60 kg, not a range of weights assumed by the Examiner

Additionally, the Examiner asserted that the "HED" should be arithmetically applied across an apparently arbitrary range of "120 pounds (54.5 kg) to 250 pounds (113.6 kg)" by multiplying each human weight by the conversion factor (e.g., 4 for mouse or 8 for rat or 10.8 for a 400 g. animal). That was also factually incorrect.

The CDER states that the conversion rates in Table 1 on page 7 assume a 60 kg human, not a range of weights. See Footnote a. It is typical for clinical trials and approved drugs to use standard doses for patients and to not arithmetically "titrate" the dose by each patient's weight. There is no factual basis for the Examiner to assert that the CDER suggests the maximum safe starting dose is actually *a range of doses* calculated for 120 to 250 pound adult healthy volunteers. It is an undisputed fact that the approved oral dose of naltrexone is 50 mg/day, irrespective of moderate variabilities in the weights of the adults. The mean weight for the adults dosed with the formula of the claims in the clinical trial as described in the specification were about 84 kg (overall), 90 kg for males and 71 kg for females. Again, the dose was not "titrated" to each patient's weight. Thus, the Examiner's decision to do so (compounded with selecting the wrong animal for conversion), resulting in an artificial range overlapping with the claimed dose was incorrect.

iii. The Correct Formula was not used

Even assuming the Examiner was correct¹ that the CDER teaches a range of starting doses designed by a weight range of human adults, the formula the Examiner used was incorrect for establishing that range. The Examiner's formula assumed the HED is the product of the animal dose and a simple ratio of animal weight to human weight. In contrast, the CDER states in Footnote a, that if one were to deviate from the assumption of a 60 kg human, the HED can be calculated according to the formula:

$$\text{HED} = \text{animal dose in mg/kg} \times (\text{animal weight in kg} / \text{human weight in kg})^{0.33}.$$

Noting the exponent in the formula, the relationship between the animal and human is not linearly related, as the Examiner assumed in her calculations.

iv. Applying the results of the CDER formula does not achieve the dose in the claims

In fact, as discussed above and in Appendix A on page 16 of the CDER, smaller rats than those used by Bartus are contemplated in Table 1 and the limitations and assumptions of the formula are discussed in detail. The application of the CDER's formula for a 50 mg/kg rat dose using 450 mg rats (Bartus) results in a starting dose of 570 mg for a 54.5 kg human (HED of 10.46 x 54.5) and a starting dose of 915 mg for a 113.6 kg human (HED of 8.05 x 113.6). Thus, if one were to apply the CDER formula as guidance to extrapolate a Sprague Dawley rat dose to humans, one would not arrive at the claimed dose range or an overlapping range.

In any event, whether one calculates the dose as alleged by the Examiner or by the reference, the starting dose to establish safety *exceeds* the therapeutic dose taught by the claim, assuming the conversion is appropriate to calculate a therapeutic (not merely safe) dose for a depot formulation.

¹ The Examiner appears to concede in the Advisory Action that she was incorrect

If the CDER was the proper standard for determining the initial safety dose for a naltrexone microsphere from the Bartus rat study, then clearly the result achieved (an efficacious dose having twice the AUC of the FDA approved oral dose) would be unexpected because the claimed ranges are substantially lower than the CDER calculations. As explained in the CDER, one typically expects the *efficacious* dose in a human needing treatment would need to be more than the initial *safety* dose for healthy adult volunteers.

Therefore, assuming the CDER is relevant to the calculations of a starting dose, the CDER suggests the invention achieved an unexpected result.

Again, the Examiner now appreciates that the math is incorrect and her initial allegation that the claimed dose is merely the straightforward application of the CDER guidelines is also incorrect. That is, the CDER was cited to provide evidence as to how one *selects* a dose. Appellant established the Examiner was *incorrect*. Nonetheless, the Examiner pursues the rejection asserting that the dose and pharmacokinetic profile are still obvious, in spite of the fact that there is no evidence relevant to *selecting* this dose or pharmacokinetic profile.

b. The CDER guidelines would not be assumed to apply to naltrexone microspheres

Notwithstanding the above, the CDER sets forth guidelines which explicitly discuss reviewing all of the animal data available with respect to a drug and applying an algorithm based on the totality of the data, selecting the most relevant animal model for a first-in-humans clinical trial. Pages 3-4. The CDER does not advocate selecting a human dose from a single published rat model.

The subject invention does not relate to a first-in-human clinical trial of naltrexone. At the time the present clinical trials were begun, naltrexone was already approved for human use at an oral dose of 50 mg/day. Bartus, for example, states that a disadvantage of oral human dosing is “widely fluctuating plasma levels” [Abstract, the Examiner’s motivation for modifying the oral treatment regimen]. At the left hand

column of page 1974 of Bartus, “daily fluctuations [in human plasma levels] may cause side effects during peak plasma levels.” This suggests that, based on the available clinical data, there may be difficulties in human bioavailability and metabolism and that high peak plasma levels should be avoided. The starting point for determining a safe and/or efficacious dose of a long acting naltrexone formulation in humans would obviously be derived from the approved oral dose. Evidence Document 4 and 8, discussed in more detail below.

Further, the CDER explicitly states the difficulties in using this algorithm, or simplified conversion formula, where human bioavailability and metabolism may differ significantly and mechanisms of toxicity may not be known. Footnote, Page 2. At Page 3, the reference explicitly states that “[t]opical, intranasal, intratissue and compartmental administration routes and depot formulations can have additional considerations.” See also Page 8.

Figure 2 of Bartus illustrates that a burst in plasma levels can be observed in rats. Considering the warnings in the CDER, one may conclude from Bartus that dosing a human patient with naltrexone microspheres would require “additional considerations” including *avoiding toxic levels* during the peak, while maintaining therapeutic levels over a period of at least two weeks or a month, with a drug known to have widely fluctuating plasma levels upon oral administration. Thus, one of skill in the art would simply not be motivated to turn to the CDER guidelines, designed to provide a simple arithmetic estimation of a safe starting dose in an initial clinical trial in adult healthy volunteers based primarily on the weight ratio of one animal model and a human (the purpose of the CDER), much less to select an efficacious therapeutic dose for a depot formulation in alcohol dependent adults (the dose in the claim).

As naltrexone is approved at a 50 mg/day oral dose, these studies would likely be determined a highly relevant study for calculating a human dose for a long acting formulation. Evidence Documents 4 and 8, discussed in more detail below.

c. Summary of the CDER

In summary, the cited CDER reference teaches an algorithm that can be used in some instances to estimate maximum safe starting doses in first-in-human clinical trials (i.e. Phase I Clinical Trials). There is no reason to conclude that one of skill in the art would be motivated to turn to the CDER to *select* an efficacious dose for a long acting formulation of 380 mg, resulting in a serum AUC of *twice* the then currently available oral dosage form.

Recognizing that the CDER did not teach the facts the Examiner alleged in the Final Office Action (that the claimed dose is a simple extrapolation of Bartus' rat dose), the Examiner asserts that the CDER provides general guidelines for establishing a human dose from animal models. However, the Examiner admits that the mathematics show that it is not true for the facts presented in this case. Thus, how the CDER supports the rejection, as compared to teaches away from the invention, is unclear.

Even if it were true that those of skill in the art may extrapolate animal models for long acting naltrexone formulations to calculate initial safe doses in humans, it does not necessarily follow that the Examiner is excused from considering whether (1) the specific pharmacokinetic profile is obvious to select (e.g., at least twice the AUC of the approved oral dose) or (2) one of skill in the art would select the claimed dose (e.g., 380 mg) to achieve the selected pharmacokinetic profile or (3) whether the results are unexpected.

Therefore, for all of the above reasons, the cited CDER reference regarding animal-to-human conversion factors for safe dosing in humans would not motivate a person having ordinary skill in the art to select the claimed dose. And, even if one were to follow the CDER guidelines as the Examiner has done, the dose would be substantially greater with an expectation of achieving a substantially lower AUC, not the inverse. Evidence Document 4.

9. Tice et al. suggest long acting formulations that achieve the same AUC as the oral dose is desirable (US Patent 6,306,425; Evidence Document 8)

Tice et al. teach an injectable long acting naltrexone formulation comprising naltrexone in a poly (D,L-lactide) matrix with a small amount of residual ethyl acetate (Abstract) administered such that the microspheres release naltrexone over a period of at least 4 weeks in human subjects where the AUC in monitoring plasma levels similar to daily dosing of a 50 mg tablet. (Column 14, lines 26-64, column 15, lines 57-61; column 16, lines 28-35; Evidence Document 4.) Tice et al. states that an objective of the long acting formulation is to allow *less* naltrexone to be administered. (Column 17, lines 1-10). Tice et al. do not teach that it is desirable to administer a dose of naltrexone that will result in 2 to 3 times the AUC of a 50 mg/day oral tablet.

10. The cited prior art, combined, does not teach the claimed invention

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be motivation to modify the reference or combine the references. Second a reasonable expectation of success must be established. Finally, the prior art must teach all of the limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The Examiner appears to assert that one of skill in the art would be motivated to modify the oral dosing regimens of Heinala because, in short, Bartus teaches disadvantages with oral dosing and suggests injection with a PLGA long acting formulation can be beneficial. However, Heinala teaches that oral naltrexone can be administered on an as needed basis when alcohol craving is high. Leavitt reinforces these teachings. A long acting formulation will administer drug even when the craving is not high. Thus, the references are simply not combinable. *In re Grasselli*, 713 F.2d 731 (Fed. Cir. 1983). The first prong of the three way test is not satisfied.

However, even if one were to combine the references and conclude that one would modify the method of Heinala by substituting a long acting formulation for a daily oral dose, Bartus, Leavitt and Heinala do not teach how much of any specific long acting formulation one should administer or that the AUC should be selected to achieve at least

twice that of the oral dose. In fact, Heinala suggests that 50 mg/day is not necessary but can be administered on an as needed basis after a couple of weeks.

The Examiner appears to state on Page 7 of the Final Action that one would necessarily formulate a long acting formulation with “higher amounts of naltrexone to accommodate the amount of time the formulation is designed to last.” Appellants do not disagree that a long acting formulation will typically have a “higher amount” of naltrexone as compared to a single oral dose (50 mg/day in this case). However, the issue is not simply whether the injectable dose should be higher than one oral dose. The issue is whether one of skill in the art would select a 190 or 380 mg dose, for example, and expect the injection of 190 or 380 mg of a naltrexone long acting formulation to achieve 2 or 3 times the serum AUC of a 50 mg/day oral dose. There is no suggestion to select a pharmacokinetic profile of twice Heinala’s dose or a reasonable expectation of success as to how to achieve such a dose. In fact, the CDER, cited by the Examiner to allege this very proposition, would suggest that, if anything, the result is not the expected result. Additionally, Tice et al. suggests that one of ordinary skill in the art would select a similar serum AUC. Evidence Document 8. The fact that a 380 mg dose of naltrexone microspheres delivered a dose at three times the AUC of oral naltrexone was unexpected. Evidence Documents 1 and 4.

Very simply, Bartus does not teach a human dose at all. Bartus presents the results in rats at 50 mg/kg. None of the prior art references cited in the rejection extrapolate a rat dose to a human dose for either oral administration or injection of naltrexone. None of the references teach or suggest that a pharmacokinetic profile of 2 or 3 times the serum AUC of a 50 mg/day oral dose is desirable. Appellant has presented evidence of unpredictability. *In re Rinehart*, 531 F.2d 1048 (CCPA 1976). Thus, the second and third prongs of the *Vaech* test are not satisfied.

11. The pharmacokinetics of the instant invention are unexpected

Heinala et al. and Leavitt teach therapeutic doses of oral naltrexone at 50 mg/day in humans. Bartus et al. teaches 50 mg/kg doses of naltrexone in an extended-release formulation and shows the dose blocks morphine-induced pain analgesia in rats. As discussed above, the limitations missing from Heinala and Leavitt are not supplied by Bartus et al.

The Examiner asserts that the guidance and motivation to provide an extended-release formulation of naltrexone is taught by Bartus et al., and that one approach for improving the effectiveness of naltrexone would be to develop an injectable formulation that would maintain plasma levels within the therapeutic range for several weeks. [Final Action, page 9, second paragraph]. Even if this were true, the references do not provide motivation to select a dose which would provide a serum AUC twice that achieved by the oral dose.

As taught by Tice et al. (Evidence Document 8), one would not choose a dose that achieves a serum AUC twice the oral dose. The teachings of Tice et al. demonstrate that the instant invention is truly unexpected. See also Evidentiary Document 4.

As in the instant application, Tice teaches injectable naltrexone microsphere compositions for the treatment of alcoholics. Bartus, however, teaches injectable naltrexone microsphere compositions for opioid receptor blockage. Compared with oral delivery, the 300 mg naltrexone PLA microsphere formulation of Tice gave an AUC that is merely 1.18 times greater than that achieved by the 50 mg/day oral administration – a value that is nearly identical to the 50 mg/day oral administration in the same study. [Tice, column 14, table, naltrexone mean F-1/Tablet ratio] Furthermore, Tice *admits* that the AUC for the daily oral dose is *similar* to that of the AUC of the injectable extended release Formulation F-1'. For example, see column 14 lines 59-64, of Tice wherein it is stated:

The data indicate that the exposure to the active naltrexone moiety is *likely to be comparable* whether taking *daily* 50-mg tablets for one month or one 300 mg of microencapsulated naltrexone by intramuscular injection of microsphere Formulation F-1' once monthly" [emphasis added].

Tice teaches that one would select a dose that would result in a comparable AUC to the oral dose. Tice does not teach that twice the AUC is desirable. Tice does not teach that about 160 to about 240 mg of naltrexone microsphere formulation or about 310 to about 480 mg of naltrexone microsphere formulation can achieve at least twice the AUC of the oral dose. Tice teaches away from the motivation to dose a patient with a sufficient amount of naltrexone to achieve twice the AUC.

The instant invention claims administering a long acting formulation comprising naltrexone to an individual wherein the "serum AUC of naltrexone is at least about two times greater than that achieved by 50 mg/day oral administration". [Specification, page 3, lines 7-11] In spite of equivalent dosing between Tice and the instant claims (e.g. 300 mg), the instant invention delivers more naltrexone than expected compared with the teachings of Tice (i.e. AUC is at least about two times greater than that achieved by 50 mg/day oral administration). Thus, in order to achieve the 1.18 AUC of Tice's 300 mg injectable formulation, which according to Tice is comparable to 50 mg/day oral administration of naltrexone (also used in Heinala and Leavitt), Appellants would need to reduce the claimed dosages by at least one half, to one third. The combined teachings of Heinala, Bartus, and Leavitt disclose nothing that adds to, clarifies, or rebuts the teachings of Tice. In this regard, the pharmacokinetics of the instant invention are not obvious and were unexpected.

12. The invention is not the result of routine optimization

Contrary to the Examiner's statement, this invention is not the result of routine optimization. [Final Action, page 11, lines 1-13; Advisory Action, Page 8] This is not a case where the human dose is selected by simply selecting the best dose. The invention arises from the unexpected result that a 380 mg dose (for example) of naltrexone

microspheres achieved a very high AUC, as compared to the oral dose (not a comparable AUC, as Tice et al. teach is desirable), and that dose is both safe and highly efficacious (in spite of the warnings of Heinala and others against higher doses of naltrexone). See the Ehrich Declaration and supporting documents. [Attached hereto as Evidence Documents #4-7] The case law cited by the Examiner does not stand for the proposition that evidence of unexpected results can be ignored simply because the invention, on some level, relates to determining a therapeutically effective dose in a pharmaceutical product.

13. The Examiner's dismissal of the evidence of unexpected results is in error

The Examiner dismisses the evidence presented in the Ehrich Declaration [Evidence Document #1 and #2] stating that the closest prior art, which is Bartus, was not compared. [Final Action, page 12, first paragraph] This statement is confusing as Bartus is relied upon as one of three secondary references. The Examiner appears to be making a substantial shift in the grounds of the rejection after final, to which the Appellant objects.

In any event, the Ehrich Declarations [Evidence Documents #1, #2, and #4-7] discuss the clinical trial results obtained from administering Vivitrex® microspheres to human patients. Bartus relates to administering Vivitrex® microspheres to Sprague Dawley rats. The Ehrich Declarations very clearly state that the expected result of administering a 380 mg naltrexone dose, for example, to humans, based on the prior art of record (including Bartus and Tice), was an AUC comparable to the oral dose at 50 mg/day. The result achieved was at least twice the expected dose. That result, as clearly stated by Dr. Ehrich, was unexpected.

The Examiner does not provide any evidence to rebut the evidence of unexpected results. Rather, the Examiner appears to assert that, if you administer a 380 mg dose of Vivitrex® microspheres to a human patient, *as claimed*, the result would inherently be the result described in the claim. The Examiner states in the Advisory Action that the Examiner is not teaching inherency but that the pharmacokinetics are an obvious property of the method steps. The Examiner bases this argument on *In re Best*, 562, F2d. 1252,

1254, 195 USPQ 430, 433 (CCPA 1977) wherein the Best court states that the claiming of a new use, new function or unknown property which is *inherently* present in the prior art does not necessarily make the claim patentable (emphasis added). So despite the Examiner's protestation that the Examiner is not trying to make the rejection based on inherency; it seems that the Examiner is in fact making the rejection based on inherency.

There is a fundamental difference between the application of inherency under §102 and the application of inherency under §103. *Trintec Indus., Inc. v TOP-U.S.A. Corp.*, 295 F.3d 1292, 296 (Fed Cir 2002) ("obviousness is not inherent anticipation"). As discussed in *In re Shetty*, 566 F.2d. 81, 86 (CCPA 1977):

As we pointed out in *In re Adams*, 53 CCPA 996, 356 F.2d. 998, 148 USPQ 742 [(1966)], the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated upon what is unknown.

The *Rijckaert* court noted that "a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 9 F3d 1531, 1534. Because the suggestion to modify references must occur prior to Appellants' date of invention, an unknown inherency cannot supply this suggestion at the required time. *Id.* A later appreciation of the relationship or the inherency does not change this analysis. *Id.*

The Examiner's mistake in this analysis is that the Examiner is taking a retrospective view of inherency in an obviousness setting which is prohibited as discussed above. Not until the present inventors *discovered* the relationship between administering a long acting naltrexone formulation by intramuscular injection and the increased AUC as compared to oral administration, did this relationship become known to anyone. Unlike inherency under §102 which does not require that the inherency be known and appreciated in the prior art at the time of the invention, inherency under §103 *still requires* that the inherency be known and appreciated in the prior art prior to the time of the invention. As per MPEP 2141.02:

Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijekaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

The case law cited by the Examiner, *In re Best*, appears to be based on the assumption that any physical property that may be considered inherent to a product, ***if used in an identical process***, renders the claimed invention obvious – even where the prior art does not teach that process. However, this reasoning has proved faulty from a jurisprudence perspective. There is later case law suggesting that that which is anticipatory is not always obvious. This is particularly true when inherency is required to provide the motivation or reasonable expectation of success in combining prior art references. One example is *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008):

“While it is commonly understood that prior art references that anticipate a claim will usually render that claim obvious, it is not necessarily true that a verdict of nonobviousness forecloses anticipation. The tests for anticipation and obviousness are different. Obviousness can be proven by combining existing prior art references, while anticipation requires all elements of a claim to be disclosed within a single reference. Moreover, obviousness requires analysis of secondary considerations of nonobviousness, while secondary considerations are not an element of a claim of anticipation. And although anticipation can be proven inherently, proof of inherent anticipation is not the same as proof of obviousness. Thus, ‘it does not follow that every technically anticipated invention would also have been obvious.’”) (internal citations omitted).

Where, as here, Bartus teaches only the administration of a 50 mg/kg dose to a rat, the unexpected result achieved by the administration of a 380 mg dose to a human (for example) must be taken into consideration. It does not appear to be disputed that the pharmacokinetics are unexpected. Accordingly, the Examiner’s dismissal of the evidence of an unexpected result as inherent is erroneous.

Indeed, the predictability of the result of a proposed combination or modification must be determined at the time the invention was made. *Ex parte Erlich*, 3USPQ2d 1011

(BPAI 1986). In contrast, the Examiner relies upon later publications (Johnson and the Press Release) to establish predictability of the result.

Again, it must be emphasized that not all limitations in the claims are taught in the prior art. The prior art does not teach that it is desirable to administer a long acting naltrexone formulation at a dose that is capable of achieving twice the AUC of the 50 mg/day oral dose.

14. The cited prior art does not enable Vivitrex microspheres

The mere naming of a product in a reference, without more, cannot constitute a description of the product. *In re Hoeksema*, 399 F.2d 269 (CCPA 1969). In the present case, while Bartus teaches that Vivitrex® microspheres were administered to rats, Bartus does not teach how to make the microspheres. Tice et al., for example, establishes that not all microsphere formulations (e.g., the exemplified PLA microsphere when administered at 300 mg) will result in an AUC of at least twice the 50 mg/day oral dose. See Evidence Document 4. The Alkermes 2003 Press Release also does not provide the requisite teaching. In contrast, the patent specification provides the teachings that provide the person of ordinary skill in the art the guidance as to how to make microspheres with this property. Absent teachings as to how to make Vivitrex® microspheres, Bartus is simply not an enabling disclosure, in view of the evidence of record.

B. Claim 7

Claim 7 is directed to a long acting formulation in a dose of about 380 mg of naltrexone. Appellant relies upon all of the arguments set forth above. Specifically, given the teachings of Tice et al. (Evidence Document 8) that a 300 mg. naltrexone-PLA microsphere achieves an AUC that approximates the 50 mg/day oral dose, a 380 mg. microsphere that achieves an AUC three times the oral daily dose is nonobvious and unexpected. Evidence Document 4.

C. Claims 6, 11 and 22

Claim 11 is directed to a method of administering the long acting formulation for a period of at least 24 weeks. Claim 22 requires a second administration at least 28 days after the first administration. Claim 6 requires the formulation to release naltrexone for at least a month. Given the teachings of Heinala et al, as discussed above, which describes the desirability of decreasing the dose after a few weeks, the art of record does not teach a method of treatment that will result in naltrexone delivery of 1 month (Claim 6), 2 months (Claim 22) or over a period of 6 months or longer (Claim 11).

(v) Claims Appendix
(Attached)

(vi) Evidence Appendix
(Attached)

The Conclusion

For the reasons discussed above, the Examiner has failed to establish that the presently claimed invention is *prima facie* obvious over the cited prior art. Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

ELMORE PATENT LAW GROUP, P.C.

/Darlene A. Vanstone/

By _____
Darlene A. Vanstone
Registration No. 35,729
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: ***October 19, 2015***

(v) **CLAIMS APPENDIX**

1. (Previously Presented) A method for treating an individual in need of naltrexone comprising the step of administering by intramuscular injection a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is at least about two times greater than that achieved by 50 mg/day oral administration, wherein the long acting formulation of naltrexone is administered only once during at least a two week period, and comprises between 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone.
- 2-5. (Cancelled)
6. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.
7. (Previously Presented) The method of claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone.
- 8-10. (Cancelled)
11. (Previously Presented) The method of claim 1 wherein the long acting formulation is administered over a period of about 24 weeks or longer.
- 12-13. (Cancelled)
14. (Previously Presented) The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency.
15. (Cancelled)
16. (Original) The method of claim 1 wherein the long acting formulation comprises a polylactide polymer or a poly lactic acid polymer.

17. (Previously Presented) The method of claim 1 wherein the long acting formulation comprises a polylactide-co-glycolide polymer.
18. (Original) The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35 % by weight.
- 19-21. (Cancelled)
22. (Previously Presented) The method of claim 11, further comprising a second administration of the long acting formulation comprising naltrexone at least about 28 days after the first administration.

(vi) **EVIDENCE APPENDIX**

Evidence Document # 1: Ehrich Declaration; 1.132 Declaration filed as Exhibit 2 in the Amendment dated February 3, 2015.

Evidence Document # 2: Table 8; filed as Exhibit 2-2 in the Amendment dated February 3, 2015.

Evidence Document # 3: CDER “Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”, July 2005; filed as Exhibit in the Amendment After Final dated July 22, 2015.

Evidence Document # 4: Ehrich Declaration; filed as “Declaration Under 1.132” in the Amendment of record dated October 5, 2009 for related application number 11/083,167 (parent).

Evidence Document # 5: Table 8; filed as Exhibit A in the Amendment of record dated October 5, 2009 for related application number 11/083,167 (parent).

Evidence Document # 6: Clinical Study Report; filed as Exhibit B in the Amendment of record dated October 5, 2009 for related application number 11/083,167 (parent).

Evidence Document # 7: Graphs; filed as Exhibit C in the Amendment of record dated October 5, 2009 for related application number 11/083,167 (parent).